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Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

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ABSTRACT

BACKGROUND

Although several studies have assessed the risk of venous thromboembolism with newer hormonal contraception, few have examined thrombotic stroke and myocardial infarction, and results have been conflicting.

METHODS

In this 15-year Danish historical cohort study, we followed nonpregnant women, 15 to 49 years old, with no history of cardiovascular disease or cancer. Data on use of hormonal contraception, clinical end points, and potential confounders were obtained from four national registries.

RESULTS

A total of 1,626,158 women contributed 14,251,063 person-years of observation, during which 3311 thrombotic strokes (21.4 per 100,000 person-years) and 1725 myocardial infarctions (10.1 per 100,000 person-years) occurred. As compared with nonuse, current use of oral contraceptives that included ethinyl estradiol at a dose of 30 to 40 μg was associated with the following relative risks (and 95% confidence intervals) for thrombotic stroke and myocardial infarction, according to progestin type: norethindrone, 2.2 (1.5 to 3.2) and 2.3 (1.3 to 3.9); levonorgestrel, 1.7 (1.4 to 2.0) and 2.0 (1.6 to 2.5); norgestimate, 1.5 (1.2 to 1.9) and 1.3 (0.9 to 1.9); desogestrel, 2.2 (1.8 to 2.7) and 2.1 (1.5 to 2.8); gestodene, 1.8 (1.6 to 2.0) and 1.9 (1.6 to 2.3); and drospirenone, 1.6 (1.2 to 2.2) and 1.7 (1.0 to 2.6), respectively. With ethinyl estradiol at a dose of 20 μg, the corresponding relative risks according to progestin type were as follows: desogestrel, 1.5 (1.3 to 1.9) and 1.6 (1.1 to 2.1); gestodene, 1.7 (1.4 to 2.1) and 1.2 (0.8 to 1.9); and drospirenone, 0.9 (0.2 to 3.5) and 0.0. For transdermal patches, the corresponding relative risks were 3.2 (0.8 to 12.6) and 0.0, and for a vaginal ring, 2.5 (1.4 to 4.4) and 2.1 (0.7 to 6.5).

CONCLUSIONS

Although the absolute risks of thrombotic stroke and myocardial infarction associated with the use of hormonal contraception were low, the risk was increased by a factor of 0.9 to 1.7 with oral contraceptives that included ethinyl estradiol at a dose of 20 μg and by a factor of 1.3 to 2.3 with those that included ethinyl estradiol at a dose of 30 to 40 μg, with relatively small differences in risk according to progestin type. (Funded by the Danish Heart Association.)

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The risk of thromboembolic complications with the use of hormonal contraception is an important issue scientifically and is relevant for counseling women about contraceptive options. Several studies have assessed the risk of venous thromboembolism associated with the use of newer hormonal contraceptive products, (i.e., those from the past 10 years)[1-8] but few studies have examined thrombotic stroke and myocardial infarction, and the results of available studies have been conflicting.[7-20] Although arterial complications are less frequent than venous complications among young women, the short-term and long-term consequences of arterial complications are often more serious.

In addition to oral contraceptive pills and intramuscular injections of depot medroxyprogesterone acetate, the options for hormonal contraception currently include a vaginal ring, transdermal patches, subcutaneous implants, and the levonorgestrel-releasing intrauterine device (IUD; known in Europe as the levonorgestrel intrauterine system). The aim of this study was to assess the risks of thrombotic stroke and myocardial infarction associated with the use of various types of hormonal contraception, according to estrogen dose, progestin type, and route of administration.

METHODS

STUDY POPULATION

We followed an open historical cohort of Danish women, 15 to 49 years old, for a 15-year period, from January 1995 through December 2009. The population was identified on the basis of data from Statistics Denmark. A unique personal identification number that is given to all Danish citizens at birth and to people who have immigrated to Denmark is used in all public registries, allowing reliable linkage of data among different registries. Statistics Denmark also provided data on length of schooling, status of education (ongoing or finished), vital status, and emigration. Data were censored at the time of death or emigration.

Approval for the study was obtained from the Danish Data Protection Agency. Because this was a registry study, the requirement for written informed consent was waived.

END POINTS

Data on clinical end points were obtained from the National Registry of Patients, which has collected discharge diagnoses from public and private Danish hospitals since 1977, and the Register of Causes of Death. The relevant diagnostic codes are listed in Table 1S in the Supplementary Appendix, available with the full text of this article at NEJM .org. We identified thrombotic stroke using the diagnostic code for cerebral infarction (which is used for both cerebral thrombosis and cerebral embolism) and the less-specific diagnostic code for "cerebral apoplexy"; thrombotic events have been found to constitute 80 to 90% of the events in young women that are classified as cerebral apoplexy.[21-23] Transient cerebral ischemic attack was not included.

To restrict the analysis to first-ever events, we excluded data from all women who had received a diagnosis of any type of venous or arterial thrombotic event before the study period (i.e., from 1977 through 1994). In addition, data from women who had gynecologic, abdominal, breast, lung, or hematologic cancer before the study period were excluded or, if any of these diseases occurred during the study period, were censored at the time of diagnosis (Table 1S in the Supplementary Appendix).

The National Registry of Patients also records surgical codes from public and private hospitals. Data from women who had undergone bilateral oophorectomy, unilateral oophorectomy two times, hysterectomy, or a sterilization procedure were either excluded at baseline or censored at the time of surgery (Table 1S in the Supplementary Appendix).

Pregnancy outcomes and gestational ages at termination were identified according to the codes specified in Table 1S in the Supplementary Appendix. Data from women were temporarily censored during pregnancy, which was defined as the period from conception through 3 months after delivery (or 1 month after abortion or termination of ectopic pregnancy). Data from women with a coagulation disorder were censored at the recorded date of the initial diagnosis (Table 1S in the Supplementary Appendix).

Finally, information about smoking habits was obtained from the National Registry of Patients. Information about whether a woman smoked was available for 480,223 women, covering 5.2 million person-years of observation (37% of risk time).

PRESCRIPTION DATA

The Register of Medicinal Products Statistics provided information, updated daily, about filled

prescriptions for oral contraceptives and other types of hormonal contraception from 1995 through 2009. We categorized the products in use according to estrogen dose, progestin type, and route of administration.

Duration of use was estimated to be the period from the date of the prescription until the end date of the last filled prescription or the date of a study event. Further details regarding the assessment of duration of use are given in a previous report.[6] From the prescription registry, we also obtained updated information about medication for the treatment of diabetes, heart arrhythmia, hypertension, and hyperlipidemia. Data from women with prescriptions for ovarian stimulants were censored at the time that such a prescription was first filled.

STATISTICAL ANALYSIS

Using Poisson regression, we calculated the estimated risks of thrombotic events, with stratification according to estrogen dose (50 μg, 30 to 40 μg, or 20 μg of ethinyl estradiol or progestin-only contraceptive), progestin type, route of administration, and duration of use (<1 year, 1 to 4 years, or >4 years). The reference group comprised nonusers (women who had never used hormonal contraception as well as former users), and the estimates of relative risk were adjusted for age, calendar year, length of schooling, educational level (ongoing or completed), and status with respect to hypertension, heart disease, diabetes, and hyperlipidemia (defined by the use or nonuse of medications for these conditions). Imputed values for missing data on smoking status were calculated with the use of standard procedures of imputation,[24] and sensitivity analyses that included imputation for smoking status were conducted (Table 2S in the Supplementary Appendix).

Tests for interactions of the different types of hormonal contraception with age and with predisposing diseases were conducted. Sensitivity analyses in which only the specific code for cerebral infarction, DI63, was included were performed for all product types. Finally, sensitivity tests were conducted for the three periods of 1995 through 1999, 2000 through 2004, and 2005 through 2009.

RESULTS

THROMBOTIC EVENTS IN THE STUDY COHORT

After the exclusion and censoring of data as specified in Figure 1, the study cohort included 1,626,158 women, with 14,251,063 person-years of observation. During this period, 3311 women had a first thrombotic stroke (1633 events [49.3%] were coded as cerebral infarction, and 1678 [50.7%] as cerebral apoplexy), and 1725 had a first myocardial infarction. The case fatality rate during the primary event or subsequent hospital stay was 1.0% for thrombotic stroke (34 of 3311 women) and 10.8% for myocardial infarction (186 of 1725).

After adjustment for calendar year, educational level, status with respect to predisposing diseases,

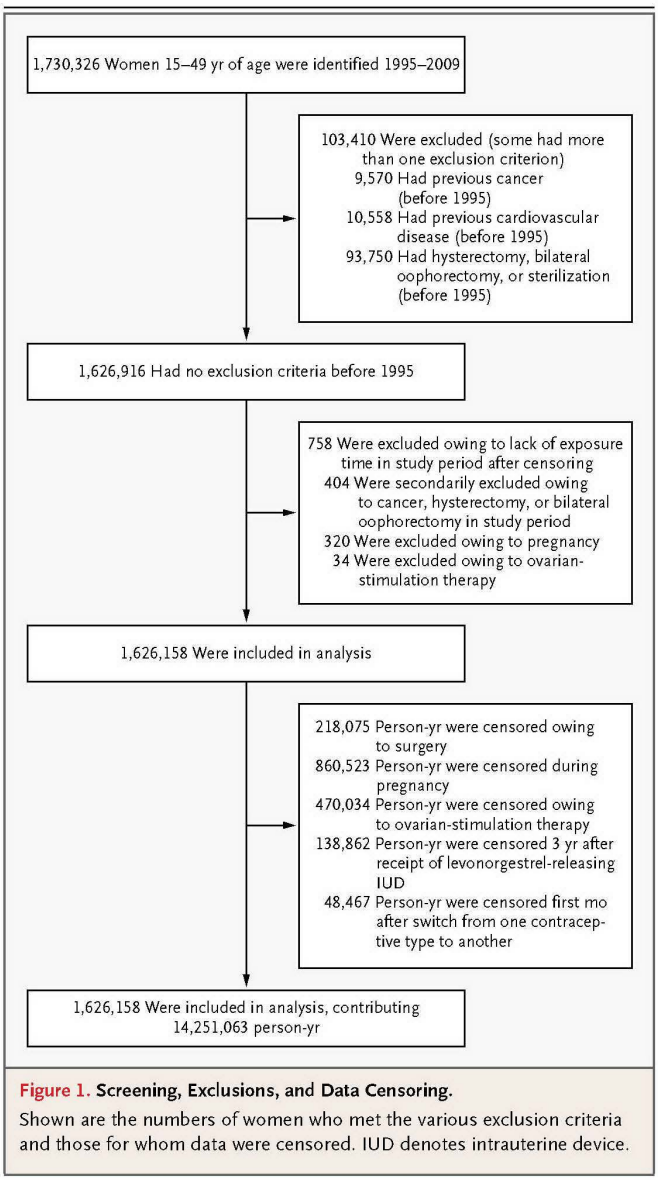

Figure 1. Screening, Exclusions, and Data Censoring.
Shown are the numbers of women who met the various exclusion criteria and those for whom data were censored. IUD denotes intrauterine device.

and use or nonuse of hormonal contraception, the incidence rates of thrombotic stroke and myocardial infarction were increased by factors of 20 and 100, respectively, in the oldest age group (45 to 49 years) as compared with the youngest age group (15 to 19 years) (Table 1).

Women with the highest level of education had about half as many thrombotic strokes and about one third as many myocardial infarctions as women with the lowest level of education (Table 1). The relative risks of thrombotic stroke and myocardial infarction, respectively, among women who filled prescriptions for medications to treat predisposing disorders, as compared with women who did not fill prescriptions for these medications, were as follows: for diabetes, 2.73 (95% confidence interval [CI], 2.32 to 3.22) and 4.66 (95% CI, 3.88 to 5.61); for hypertension, 2.32 (95% CI, 2.14 to 2.50) and 2.17 (95% CI, 1.95 to 2.42); and for hyperlipidemia, 2.11 (95% CI, 1.74 to 2.56) and 1.88 (95% CI, 1.46 to 2.41) (Table 1).

HORMONAL CONTRACEPTION AND ARTERIAL THROMBOSIS

In 4.9 million person-years of use of hormonal contraception, 1051 women had a thrombotic

Table 1. Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Nonpregnant Danish Women, According to Age, Calendar Year, Educational Level, and Predisposing Risk Factors, 1995–2009.

Variable	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
Age							
15–19 yr	2,075,087	70	3.4	0.05 (0.04–0.06)	9	0.4	0.01 (0.01–0.02)
20–24 yr	1,961,761	110	5.6	0.07 (0.06–0.09)	13	0.7	0.02 (0.01–0.03)
25–29 yr	1,906,954	201	10.5	0.16 (0.13–0.18)	41	2.2	0.06 (0.04–0.08)
30–34 yr	2,053,357	317	15.4	0.26 (0.23–0.30)	102	5.0	0.15 (0.12–0.18)
35–39 yr	2,149,752	501	23.3	0.40 (0.36–0.44)	262	12.2	0.36 (0.31–0.41)
40–44 yr	2,104,119	825	39.2	0.65 (0.59–0.71)	534	25.4	0.71 (0.64–0.80)
45–49 yr	2,000,033	1287	64.4	1.00	764	38.2	1.00
Year							
1995	1,110,157	183	16.5	1.00	108	9.7	1.00
1996	1,082,648	172	15.9	0.91 (0.74–1.12)	105	9.7	0.94 (0.72–1.23)
1997	1,052,178	192	18.3	1.02 (0.83–1.25)	104	9.9	0.94 (0.72–1.23)
1998	1,026,757	168	16.4	0.89 (0.72–1.10)	100	9.7	0.90 (0.69–1.19)
1999	1,001,828	219	21.9	1.16 (0.95–1.41)	109	10.9	0.98 (0.75–1.28)
2000	981,241	211	21.5	1.11 (0.91–1.36)	125	12.7	1.12 (0.87–1.45)
2001	959,246	218	22.7	1.15 (0.94–1.40)	133	13.9	1.19 (0.92–1.53)
2002	938,943	224	23.9	1.18 (0.97–1.44)	143	15.2	1.27 (0.99–1.64)
2003	918,924	236	25.7	1.25 (1.03–1.51)	148	16.1	1.32 (1.03–1.70)
2004	903,351	232	25.7	1.22 (1.00–1.48)	126	14.0	1.12 (0.87–1.45)
2005	883,911	243	27.5	1.28 (1.06–1.56)	117	13.2	1.05 (0.80–1.36)
2006	867,957	273	31.5	1.45 (1.20–1.75)	102	11.8	0.91 (0.69–1.20)
2007	852,227	251	29.5	1.34 (1.10–1.62)	121	14.2	1.09 (0.84–1.42)
2008	843,664	232	27.5	1.24 (1.02–1.51)	87	10.3	0.78 (0.59–1.04)
2009	828,032	257	31.0	1.39 (1.15–1.69)	97	11.7	0.89 (0.67–1.18)

Table 1. (Continued.)

Variable	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*	No. of Events	Incidence Rate	Adjusted Relative Risk (95% CI)*
			no. of events/ 100,000 person-yr			*no. of events/ 100,000 person-yr*	
Educational level†							
Elementary school completed	3,808,238	1355	35.6	2.06 (1.85–2.29)	816	21.4	3.08 (2.63–3.61)
High school ongoing or completed	1,638,840	198	12.1	1.1 (0.93–1.31)	72	4.4	1.31 (0.99–1.72)
High school and middle education ongoing or completed	3,778,853	1080	28.6	1.4 (1.26–1.56)	587	15.5	1.87 (1.59–2.20)
High school and long education ongoing or completed	2,383,029	470	19.7	1.00	194	8.1	1.00
Unknown	2,642,102	208	7.9	1.88 (1.54–2.28)	56	2.1	2.36 (1.72–3.24)
Risk factor							
Diabetes‡	123,264	186	150.9	2.73 (2.32–3.22)	159	129.0	4.66 (3.88–5.61)
Hypertension‡	1,343,081	1039	77.4	2.32 (2.14–2.50)	581	43.3	2.17 (1.95–2.42)
Hyperlipidemia‡	63,111	139	220.3	2.11 (1.74–2.56)	85	134.7	1.88 (1.46–2.41)
Arrhythmia‡	69,752	68	97.5	1.80 (1.41–2.29)	54	77.4	2.56 (1.95–3.37)
Smoking§	1,195,490	204	17.1	1.57 (1.31–1.87)	112	9.37	3.62 (2.69–4.87)

* Relative risks were adjusted for hormonal contraception and the other variables included in the table.
† In Denmark, middle education is defined as 4 years of education after high school, and long education as 5 to 6 years of education after high school.
‡ Risk factors were identified on the basis of the use of medications that are used to treat these conditions.
§ Data on smoking are for the subpopulation with available information (480,223 women, covering 5.2 million person-years of observation and including about 1.2 million person-years among smokers).

stroke and 497 had a myocardial infarction; the crude incidence rates were 21.4 and 10.1 per 100,000 person-years, respectively. The corresponding incidence rates in 9,336,662 person-years of nonuse, during which 2260 women had a thrombotic stroke and 1228 had a myocardial infarction, were 24.2 and 13.2 per 100,000 person-years, with the higher rates primarily due to older age and a higher frequency of predisposing conditions among nonusers (Table 2).

The risk among previous users was similar to the risk among women who had never used hormonal contraception. The rate ratio for thrombotic stroke among previous users, as compared with women who had never used hormonal contraception, was 1.04 (95% CI, 0.95 to 1.15), and for myocardial infarction, 0.99 (95% CI, 0.86 to 1.13).

After stratifying the data for current users of hormonal contraception according to estrogen dose, progestin type, and route of administration, we estimated the crude incidence rates and adjusted relative risks of thrombotic events for users as compared with nonusers (Table 2). The estimated relative risks of thrombotic stroke and myocardial infarction among users of combined oral contraceptive pills that included ethinyl estradiol at a dose of 30 to 40 μg did not differ significantly according to the type of progestin, ranging from 1.40 to 2.20 for stroke and from 1.33 to 2.28 for myocardial infarction. For both end points, the risk estimates were lowest with contraceptive pills that included norgestimate or cyproterone acetate and were highest with those that included norethindrone or desogestrel (Table 2).

For women who used desogestrel with a reduced dose of ethinyl estradiol (20 μg), as compared with nonusers, the relative risks of thrombotic stroke and myocardial infarction were 1.53 (95% CI, 1.26 to 1.87) and 1.55 (95% CI, 1.13 to 2.13), respectively. For women who used drospirenone with ethinyl estradiol at a dose of 20 μg, the relative risk of thrombotic stroke was 0.88

Table 2. Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Users of Different Types of Hormonal Contraception, as Compared with Nonusers.*

Type of Hormonal Contraception	No. of Person-yr	Thrombotic Stroke			Myocardial Infarction		
		No. of Events	Incidence Rate (no. of events/100,000 person-yr)	Adjusted Relative Risk (95% CI)†	No. of Events	Incidence Rate (no. of events/100,000 person-yr)	Adjusted Relative Risk (95% CI)†
None	9,336,662	2260	24.2	1.00	1228	13.2	1.00
Ethinyl estradiol, 50 μg							
Norethindrone	43,234	9	20.8	1.27 (0.66–2.45)	11	25.4	2.74 (1.51–4.97)
Levonorgestrel	54,474	32	58.7	2.26 (1.59–3.20)	36	66.1	4.31 (3.09–6.00)
Ethinyl estradiol, 30 to 40 μg							
Norethindrone	126,984	28	22.1	2.17 (1.49–3.15)	14	11.0	2.28 (1.34–3.87)
Levonorgestrel	460,559	144	31.3	1.65 (1.39–1.95)	91	19.8	2.02 (1.63–2.50)
Norgestimate	453,536	78	17.2	1.52 (1.21–1.91)	28	6.2	1.33 (0.91–1.94)
Desogestrel	313,560	99	31.6	2.20 (1.79–2.69)	43	13.7	2.09 (1.54–2.84)
Gestodene	1,318,962	285	21.6	1.80 (1.58–2.04)	133	10.1	1.94 (1.62–2.33)
Drospirenone	286,770	52	18.1	1.64 (1.24–2.18)	18	6.3	1.65 (1.03–2.63)
Cyproterone acetate	187,145	29	15.5	1.40 (0.97–2.03)	12	6.4	1.47 (0.83–2.61)
Ethinyl estradiol, 20 μg							
Desogestrel	695,603	105	15.1	1.53 (1.26–1.87)	40	5.8	1.55 (1.13–2.13)
Gestodene	564,268	88	15.6	1.70 (1.37–2.12)	21	3.7	1.20 (0.77–1.85)
Drospirenone	23,056	2	8.7	0.88 (0.22–3.53)	0	0	0 (0.00–12.99)
Progestin only							
Norethindrone	85,874	28	32.6	1.35 (0.93–1.96)	9	10.5	0.81 (0.42–1.56)
Levonorgestrel	8,556	1	11.7	0.44 (0.06–3.12)	0	0	0 (0.00–35.01)
Desogestrel	29,185	9	30.8	1.37 (0.71–2.63)	4	13.7	1.46 (0.55–3.90)
Levonorgestrel IUD	184,875	45	24.3	0.73 (0.54–0.98)	31	16.8	1.02 (0.71–1.46)
Implant	24,954	3	12.0	0.88 (0.28–2.72)	3	12.0	2.14 (0.69–6.65)
Other							
Patch	4,748	2	42.1	3.15 (0.79–12.60)	0	0	0 (0.00–63.10)
Vaginal ring	38,246	12	31.4	2.49 (1.41–4.41)	3	7.8	2.08 (0.67–6.48)

* IUD denotes intrauterine device.
† Relative risks were adjusted for age, educational level, calendar year, and risk factors.

(95% CI, 0.22 to 3.53); there were no myocardial infarctions in this group.

None of the progestin-only products, including the levonorgestrel-releasing IUD and the subcutaneous implants, significantly increased the risk of thrombotic stroke or myocardial infarction (Table 2), but the numbers were small for several of these groups. In contrast, the relative risk of thrombotic stroke was 3.15 (95% CI, 0.79 to 12.6) among women who used contraceptive patches and 2.49 (95% CI, 1.41 to 4.41) among those who used a vaginal ring. Numbers of myocardial infarctions were too low to provide reliable estimates.

An analysis adjusted for differences in progestin type, age, and calendar year showed that combined oral contraceptives with doses of ethinyl estradiol of 20 μg, 30 to 40 μg, and 50 μg were associated with a relative risk of thrombotic

stroke of 1.60 (95% CI, 1.37 to 1.86), 1.75 (95% CI, 1.61 to 1.92), and 1.97 (95% CI, 1.45 to 2.66), respectively (P=0.24 for trend). The corresponding relative risks for myocardial infarction were 1.40 (95% CI, 1.07 to 1.81), 1.88 (95% CI, 1.66 to 2.13), and 3.73 (95% CI, 2.78 to 5.00), respectively (P<0.001 for trend).

SMOKING

Information about whether a woman smoked was available for 480,223 women, covering 5.2 million person-years of observation and including 1.2 million person-years among smokers. Smoking status was known for 582 women who had a thrombotic stroke and for 193 women who had a myocardial infarction. For women who smoked as compared with those who did not, the relative risks of thrombotic stroke and myocardial infarction were 1.57 (95% CI, 1.31 to 1.87) and 3.62 (95% CI, 2.69 to 4.87), respectively. However, smoking had no confounding influence on the relative risk of arterial thrombosis among users of different types of hormonal contraception, after adjustment for age and predisposing conditions, and the results of an analysis in which smoking status was imputed were similar to the results with no imputation of smoking status (Table 2S in the Supplementary Appendix).

SENSITIVITY ANALYSES

There was no consistent interaction between the use of oral contraceptives and the relative risk of thrombotic stroke or myocardial infarction in different age groups, and there were no trends according to duration of use for either end point (Table 3). The sensitivity analysis, which included only women with the diagnostic code for cerebral infarction, provided slightly higher risk estimates than our primary analysis of thrombotic stroke (Table 3S in the Supplementary Appendix). Although the incidence rate of thrombotic stroke increased over time, we could not detect any consistent change in the estimated relative risks of the two end points for four different product groups during the three periods of 1995 through 1999, 2000 through 2004, and 2005 through 2009 (data not shown). We found no interaction between the use of hormonal contraception and predisposing disease for the risk of thrombotic stroke or myocardial infarction. The age distribution according to product group is shown in Figure 2S in the Supplementary Appendix.

DISCUSSION

The rates of thrombotic stroke and myocardial infarction increased by factors of 20 and 100, respectively, with increasing age. Only small differences in risk were observed between women who took combination pills containing intermediate-dose ethinyl estradiol (30 to 40 μg) and those who took low-dose ethinyl estradiol (20 μg), and only minor variations in risk were associated with different progestin types.

The increased incidence of thrombotic stroke over the 15-year study period probably reflects improvements in the diagnostic equipment, allowing the detection of small cerebral infarctions, rather than a real increase in incidence. The steep increase in incidence with older age has been shown in several previous studies.[9-11,25] This information has clinical implications, given that arterial thrombosis after the age of 30 years is more frequent and has more serious consequences than venous thrombosis.[6] The risk of arterial thrombosis should therefore be considered together with the risk of venous thrombosis when hormonal contraception is prescribed.

The relative risk of thrombotic stroke of 1.4 to 2.2 among current users of oral contraceptives containing ethinyl estradiol at a dose of 30 to 40 μg is slightly lower than previously reported (Table 4S in the Supplementary Appendix). In a multicenter World Health Organization study, Poulter et al. found that women who used second-generation oral contraceptive pills with levonorgestrel, as compared with nonusers, had a relative risk of thrombotic stroke of 2.7 (95% CI, 1.8 to 4.1) and users of third-generation pills had a relative risk of 1.8 (95% CI, 0.6 to 5.2).[9] Among women who had their blood pressure measured before obtaining a prescription, these risk estimates were reduced to 2.0 (95% CI, 1.1 to 3.6) and 1.6 (95% CI, 0.4 to 6.6), respectively.[9] These estimates are closer to ours, perhaps because a majority of Danish women have their blood pressure checked before obtaining prescriptions for oral contraceptives.

In our secondary analysis, which included only the code for cerebral infarction, we observed a slightly higher relative risk of stroke associated with hormonal contraception, as compared with our primary analysis. This difference may have been due to the inclusion of 15 to 20% of hemorrhagic strokes in the primary analysis that were

Table 3. Relative Risk of Thrombotic Stroke and Myocardial Infarction among Users of Selected Types of Combined Oral Contraception with Ethinyl Estradiol at a Dose of 30 to 40 μg, as Compared with Nonusers, According to Duration of Use.

Type of Hormonal Contraception	No. of Person-yr	Thrombotic Stroke		Myocardial Infarction	
		No. of Events	Relative Risk (95% CI)	No. of Events	Relative Risk (95% CI)
Nonuse	9,336,662	2260	1.00	1228	1.00
Levonorgestrel					
<1 yr	175,205	45	1.72 (1.28–2.32)	24	1.91 (1.27–2.87)
1–4 yr	190,598	49	1.50 (1.13–1.99)	32	1.95 (1.37–2.77)
>4 yr	94,756	50	1.74 (1.31–2.30)	35	2.26 (1.61–3.17)
Desogestrel					
<1 yr	131,061	31	1.91 (1.34–2.73)	10	1.45 (0.78–2.71)
1–4 yr	130,633	38	2.13 (1.54–2.94)	21	2.67 (1.73–4.12)
>4 yr	51,866	30	2.48 (1.73–3.56)	12	2.09 (1.18–3.69)
Gestodene					
<1 yr	541,756	107	1.91 (1.57–2.33)	44	1.97 (1.45–2.67)
1–4 yr	554,721	96	1.53 (1.24–1.88)	47	1.83 (1.36–2.46)
>4 yr	222,485	82	1.86 (1.49–2.33)	42	2.08 (1.52–2.84)
Drospirenone					
<1 yr	139,543	30	2.00 (1.38–2.88)	8	1.64 (0.81–3.30)
1–4 yr	116,873	11	0.84 (0.46–1.52)	8	1.91 (0.95–3.84)
>4 yr	30,353	11	2.20 (1.21–3.98)	2	1.12 (0.28–4.50)
All above types					
<1 yr	987,564	213	1.90 (1.64–2.20)	86	1.85 (1.48–2.31)
1–4 yr	992,825	194	1.55 (1.33–1.80)	108	1.99 (1.63–2.43)
>4 yr	399,461	173	1.93 (1.65–2.26)	91	2.11 (1.70–2.62)

coded as cerebral apoplexy, supporting the finding that oral contraception is associated with a lower risk of cerebral hemorrhage than of cerebral infarction.[26-28]

Heinemann et al. reported a case–control study showing that women who used second-generation oral contraceptive pills with levonorgestrel or norgestimate had a risk of thrombotic stroke that was 2.7 times (95% CI, 1.5 to 4.6) as high as the risk among nonusers and those who used third-generation pills had a risk that was 3.4 times (95% CI, 1.9 to 6.4) as high.[10] These estimates are higher than those reported in the present study.

In a previous Danish case–control study that covered the period from 1994 through 1998, we found that users of second-generation oral contraceptive pills had a risk of cerebral thromboembolism that was 2.2 times (95% CI, 1.6 to 3.0) as high as the risk among nonusers.[11] The odds ratio for cerebral thromboembolism among users of third-generation pills was 1.4 (95% CI, 1.0 to 1.9). These results are in accordance with our current findings.

Gronich et al. recently found that oral contraceptives with drospirenone and ethinyl estradiol at a dose of 30 μg were associated with the same magnitude of risk as second-generation and third-generation pills with the same dose of estrogen[8] — results that are in agreement with ours. Our data suggest a relatively high risk of thrombotic stroke with the use of a vaginal ring and possibly with the use of transdermal patches. Until further evidence emerges, one might expect a higher risk of thrombotic stroke with parenteral administra-

tion than with oral administration (estrogen combined with progestin).

There was a relatively high correlation in risk estimates for thrombotic stroke and myocardial infarction among the different product groups — a finding that increases the likelihood that the observed differences in risk were real rather than random variations. One previous study showed a tendency toward a higher relative risk of myocardial infarction with the use of third-generation, as compared with second-generation, oral contraceptives,[16] three showed the opposite result,[13,14,19] and one showed no difference[18] (Table 4S in the Supplementary Appendix). We found no consistent difference according to progestin type, but the risk decreased with lower doses of estrogen. We also found that low-dose pills were associated with approximately a 50% increase in the risk of myocardial infarction and intermediate-dose pills with up to a 100% increase in risk.

A crucial point in all registry-based studies is the validity of the diagnostic codes. In our 2002 study, we excluded 5.0% of women with a diagnosis of thrombotic stroke because of an absence of confirmation from the patient or the treating department.[11] The diagnosis of myocardial infarction has been found to be valid in 93.6% of patients of all ages,[29] and the percentage is probably higher among young patients. Any diagnostic misclassification may have led to an underestimation of the relative risks among current users. Another limitation is that, for some women, there may have been a time lag between the date of the prescription and the date the medication was actually started.

We had detailed and valid exposure information because the prescriptions were transferred electronically from the pharmacies by bar codes linked to the personal identification number. We were thus free of recall bias, an issue of concern in all retrospective case–control studies. The national cohort design ensured a large sample and allowed the calculation of risk estimates for specific product groups according to estrogen dose, progestin type, and route of administration — the majority with an acceptable precision. The design also avoided the problem of sample reduction due to nonresponse in survey studies, ensuring a high external validity.

For the levonorgestrel-releasing IUD, we had information only about the dates that the women received the IUD. Although this IUD has a valid period of 5 years, many women have it removed before the expiration date. Because of this uncertainty, we censored data for women with a levonorgestrel-releasing IUD after 3 years, unless another prescription for hormonal contraception was filled before that date. This approach reduced our exposure time for this specific product but increased the probability that the women who were classified as having a levonorgestrel-releasing IUD actually did have it.

Data on body-mass index were not available, but body-mass index was not a confounder in our previous study.[11] Smoking, although an important risk factor for arterial thrombosis, had no confounding influence in either this study or our previous one, in which we had more comprehensive information about this potential confounder. Therefore, it is not likely that our results were strongly influenced by incomplete data on these two potential confounders. However, in the absence of definitive data, we cannot be sure whether there would be an interaction with smoking.

In conclusion, women who used oral contraceptives with ethinyl estradiol at a dose of 30 to 40 μg had a risk of arterial thrombosis that was 1.3 to 2.3 times as high as the risk among nonusers, and women who used pills with ethinyl estradiol at a dose of 20 μg had a risk that was 0.9 to 1.7 times as high, with only small differences according to progestin type. We estimate that among 10,000 women who use desogestrel with ethinyl estradiol at a dose of 20 μg for 1 year, 2 will have arterial thrombosis and 6.8 women taking the same product will have venous thrombosis. Although venous thrombosis is three to four times as frequent as arterial thrombosis among young women, the latter is associated with higher mortality and more serious consequences for the survivors. Therefore, these figures should be taken into account when prescribing hormonal contraception.

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